PATENT COOPERATION TREATY

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To: J. PETER FASSE
FISH AND RICHARDSON, P.C.
225 FRANKLIN STREET
BOSTON, MA 02110-2804

RECEIVED
JAN 25 2001
FISH & RICHARDSON, P.C.
BOSTON OFFICE

PCT

NOTIFICATION OF TRANSMITTAL OF INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Rule 71.1)

Date of Mailing *(day/month/year)*	19 JAN 2001
Applicant's or agent's file reference: 00786/400WO2	IMPORTANT NOTIFICATION

International application No.	International filing date *(day/month/year)*	Priority Date *(day/month/year)*
PCT/US99/18022	06 AUGUST 1999	07 AUGUST 1998

Applicant
THE GENERAL HOSPITAL CORPORATION

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international application.

2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.

3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.

4. **REMINDER**

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices)(Article 39(1))(see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

Docketing Required *
Entered By PracticeSystems
Reviewed By Billing Secretary

Name and mailing address of the IPEA/US	Authorized officer
Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231	OLGA CHERNYSHEV TERRY J. DEY PARALEGAL SPECIALIST TECHNOLOGY CENTER 1600
Facsimile No. (703) 305-3230	Telephone No. (703) 308-0196

Form PCT/IPEA/416 (July 1992) *

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference 00786/400WO1	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/US99/18022	International filing date *(day/month/year)* 06 AUGUST 1999	Priority date *(day/month/year)* 07 AUGUST 1998
International Patent Classification (IPC) or national classification and IPC Please See Supplemental Sheet.		
Applicant THE GENERAL HOSPITAL CORPORATION		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 4 sheets.

   ☐ This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority. (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 0 sheets.

3. This report contains indications relating to the following items:

   I ☒ Basis of the report

   II ☐ Priority

   III ☐ Non-establishment of report with regard to novelty, inventive step or industrial applicability

   IV ☐ Lack of unity of invention

   V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

   VI ☐ Certain documents cited

   VII ☐ Certain defects in the international application

   VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
07 MARCH 2000	03 JANUARY 2001
Name and mailing address of the IPEA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231	Authorized officer OLGA CHERNYSHEV
Facsimile No. (703) 305-3230	Telephone No. (703) 308-0196

TERRY J. DEY
PARALEGAL SPECIALIST
TECHNOLOGY CENTER 1600

Form PCT/IPEA/409 (cover sheet) (July 1998) ★

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.
PCT/US99/18022

I. Basis of the report

1. With regard to the **elements** of the international application:*

[X] the international application as originally filed

[X] the description:
pages 1-31 , as originally filed
pages NONE , filed with the demand
pages NONE , filed with the letter of _____

[X] the claims:
pages 32-34 , as originally filed
pages NONE , as amended (together with any statement) under Article 19
pages NONE , filed with the demand
pages NONE , filed with the letter of _____

[X] the drawings:
pages 1 , as originally filed
pages NONE , filed with the demand
pages NONE , filed with the letter of _____

[X] the sequence listing part of the description:
pages 1-3 , as originally filed
pages NONE , filed with the demand
pages NONE , filed with the letter of _____

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.
These elements were available or furnished to this Authority in the following language _____ which is:

[ ] the language of a translation furnished for the purposes of international search (under Rule 23.1(b)).

[ ] the language of publication of the international application (under Rule 48.3(b)).

[ ] the language of the translation furnished for the purposes of international preliminary examination (under Rules 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

[X] contained in the international application in printed form.

[X] filed together with the international application in computer readable form.

[ ] furnished subsequently to this Authority in written form.

[ ] furnished subsequently to this Authority in computer readable form.

[ ] The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

[ ] The statement that the information recorded in computer readable form is identical to the writen sequence listing has been furnished.

4. [X] The amendments have resulted in the cancellation of:

[X] the description, pages NONE

[X] the claims, Nos. NONE

[X] the drawings, sheets/~~fig~~ NONE

5. [ ] This report has been drawn as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).**

** Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17).*

***Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.*

International application No.
PCT/US99/18022

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. statement

Novelty (N)	Claims	1-18	YES
	Claims	19-24	NO
Inventive Step (IS)	Claims	NONE	YES
	Claims	1-24	NO
Industrial Applicability (IA)	Claims	1-24	YES
	Claims	NONE	NO

2. citations and explanations (Rule 70.7)

Claims 19-24 lack novelty under PCT Article 33(2) as being anticipated by FABER-ELMAN et al.

FABER-ELMAN et al. disclose epidermal growth factor, transforming growth factor- α (TGF-α), and heparin-binding EGF (HB-EGF) (see page 163, column 2, paragraph 2). Further, claim 24 also lacks novelty because FABER-ELMAN et al. teach pharmaceutical compositions (see page 169, column 1, third paragraph). The claims include intended use language, which does not further limit or define the claims directed to polypeptides. Therefore, the polypeptides disclosed in FABER-ELMAN et al. meet the limitations of the claims.

Claims 1-18 lack an inventive step under PCT Article 33(3) as being obvious over FABER-ELMAN et al.

FABER-ELMAN et al. teach participation of growth factors, including epidermal growth factor (EGF), transforming growth factor-α (TGF-α) and heparin-binding EGF (HB-EGF) in regeneration of central nervous system nerves *in vitro*, as well as their role in neuronal survival and wound healing (see Figure 2 and pages 162, 167). FABER-ELMAN et al. further suggest that these polypeptides are promising candidates for therapeutic administration (see page 169). FABER-ELMAN et al. do not disclose administration of these growth factors to a patient for the treatment of a neurological deficit.

It would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to administer the growth factors of FABER-ELMAN et al. to a patient for the treatment of a neurological deficit because FABER-ELMAN et al. teach that these growth factors promote neuronal regeneration and FABER-ELMAN et al. teach that administration of these growth factors would be useful for therapy in patients. One of ordinary skill in the art would have a reasonable expectation of success in treatment of a neurological deficit by administration of these growth factors because the *in vitro* results of FABER-ELMAN et al. would be (Continued on Supplemental Sheet.)

Supplemental Box
(To be used when the space in any of the preceding boxes is not sufficient)

Continuation of: Boxes I - VIII

CLASSIFICATION:
The International Patent Classification (IPC) and/or the National classification are as listed below:
IPC(7): A61K 38/16, 38/18, 38/19; C07K 14/00, 14/475, 14/485, 14/495, 14/52 and US Cl.: 514/2, 12; 530/300, 350, 399; 424/85.1

V. 2. REASONED STATEMENTS - CITATIONS AND EXPLANATIONS (Continued):
considered predictive of *in vivo* administration.

Claims 1-24 meet the criteria set out in PCT Article 33(4), because one of ordinary skill in the art would find the therapeutic methods of the invention useful for treatment of neurological deficit.

---------- NEW CITATIONS ----------
NONE

PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 : A61K 38/16, 38/18, 38/19, C07K 14/00, 14/475, 14/485, 14/495, 14/52 — A1

(11) International Publication Number: **WO 00/07611**

(43) International Publication Date: 17 February 2000 (17.02.00)

(21) International Application Number: PCT/US99/18022

(22) International Filing Date: 6 August 1999 (06.08.99)

(30) Priority Data:
60/095,830 7 August 1998 (07.08.98) US

(63) Related by Continuation (CON) or Continuation-in-Part (CIP) to Earlier Application
US 60/095,830 (CON)
Filed on 7 August 1998 (07.08.98)

(71) Applicant *(for all designated States except US)*: THE GENERAL HOSPITAL CORPORATION [US/US]; 55 Fruit Street, Boston, MA 02114 (US).

(72) Inventor; and
(75) Inventor/Applicant *(for US only)*: FINKLESTEIN, Seth, P. [US/US]; 308a Hunnewell Street, Needham, MA 02494 (US).

(74) Agent: FASSE, J., Peter; Fish & Richardson, P.C., 225 Franklin Street, Boston, MA 02110–2804 (US).

(81) Designated States: CA, JP, US, European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).

Published
With international search report.
Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.

(54) Title: TREATMENT OF CENTRAL NERVOUS SYSTEM ISCHEMIA OR TRAUMA WITH EPIDERMAL GROWTH FACTOR–LIKE POLYPEPTIDES

(57) Abstract

The present invention features methods for preventing, reducing, or eliminating a neurological deficit caused by an injury to the central nervous system (CNS). The methods can be carried out, for example, by administering a polypeptide in the epidermal growth factor (EGF) family to a patient who has such a deficit.

PATENT COOPERATION TREATY

PCT/US99/18022

JRG
JPF

From the INTERNATIONAL BUREAU

PCT

NOTICE INFORMING THE APPLICANT OF THE COMMUNICATION OF THE INTERNATIONAL APPLICATION TO THE DESIGNATED OFFICES

(PCT Rule 47.1(c), first sentence)

To:
FASSE, J., Peter
Fish & Richardson, P.C.
225 Franklin Street
Boston, MA 02110-2804
ÉTATS-UNIS D'AMÉRIQUE

Date of mailing (day/month/year)	
17 February 2000 (17.02.00)	
Applicant's or agent's file reference	**IMPORTANT NOTICE**
00786/400WO2	

International application No.	International filing date (day/month/year)	Priority date (day/month/year)
PCT/US99/18022	06 August 1999 (06.08.99)	07 August 1998 (07.08.98)

Applicant
THE GENERAL HOSPITAL CORPORATION et al

1. Notice is hereby given that the International Bureau has communicated, as provided in Article 20, the international application to the following designated Offices on the date indicated above as the date of mailing of this Notice:
   EP,JP,US

   In accordance with Rule 47.1(c), third sentence, those Offices will accept the present Notice as conclusive evidence that the communication of the international application has duly taken place on the date of mailing indicated above and no copy of the international application is required to be furnished by the applicant to the designated Office(s).

2. The following designated Offices have waived the requirement for such a communication at this time:
   CA

   The communication will be made to those Offices only upon their request. Furthermore, those Offices do not require the applicant to furnish a copy of the international application (Rule 49.1(a-bis)).

3. Enclosed with this Notice is a copy of the international application as published by the International Bureau on
   17 February 2000 (17.02.00) under No. WO 00/07611

REMINDER REGARDING CHAPTER II (Article 31(2)(a) and Rule 54.2)

If the applicant wishes to postpone entry into the national phase until 30 months (or later in some Offices) from the priority date, a **demand for international preliminary examination** must be filed with the competent International Preliminary Examining Authority before the expiration of 19 months from the priority date.

It is the applicant's sole responsibility to monitor the 19-month time limit.

Note that only an applicant who is a national or resident of a PCT Contracting State which is bound by Chapter II has the right to file a demand for international preliminary examination.

REMINDER REGARDING ENTRY INTO THE NATIONAL PHASE (Article 22 or 39(1))

If the applicant wishes to proceed with the international application in the **national phase**, he must, within 20 months or 30 months, or later in some Offices, perform the acts referred to therein before each designated or elected Office.

For further important information on the time limits and acts to be performed for entering the national phase, see the Annex to Form PCT/IB/301 (Notification of Receipt of Record Copy) and Volume II of the PCT Applicant's Guide.

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland	Authorized officer J. Zahra
Facsimile No. (41-22) 740.14.35	Telephone No. (41-22) 338.83.38

Form PCT/IB/308 (July 1996)

3100077

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	**ES**	Spain	**LS**	Lesotho	**SI**	Slovenia
AM	Armenia	**FI**	Finland	**LT**	Lithuania	**SK**	Slovakia
AT	Austria	**FR**	France	**LU**	Luxembourg	**SN**	Senegal
AU	Australia	**GA**	Gabon	**LV**	Latvia	**SZ**	Swaziland
AZ	Azerbaijan	**GB**	United Kingdom	**MC**	Monaco	**TD**	Chad
BA	Bosnia and Herzegovina	**GE**	Georgia	**MD**	Republic of Moldova	**TG**	Togo
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CA	Canada	**IT**	Italy	**MX**	Mexico	**UZ**	Uzbekistan
CF	Central African Republic	**JP**	Japan	**NE**	Niger	**VN**	Viet Nam
CG	Congo	**KE**	Kenya	**NL**	Netherlands	**YU**	Yugoslavia
CH	Switzerland	**KG**	Kyrgyzstan	**NO**	Norway	**ZW**	Zimbabwe
CI	Côte d'Ivoire	**KP**	Democratic People's Republic of Korea	**NZ**	New Zealand		
CM	Cameroon			**PL**	Poland		
CN	China	**KR**	Republic of Korea	**PT**	Portugal		
CU	Cuba	**KZ**	Kazakstan	**RO**	Romania		
CZ	Czech Republic	**LC**	Saint Lucia	**RU**	Russian Federation		
DE	Germany	**LI**	Liechtenstein	**SD**	Sudan		
DK	Denmark	**LK**	Sri Lanka	**SE**	Sweden		
EE	Estonia	**LR**	Liberia	**SG**	Singapore		

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US99/18022

A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) :Please See Extra Sheet.
US CL :514/2, 12; 530/300, 350, 399; 424/85.1
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 514/2, 12; 530/300, 350, 399; 424/85.1

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

NONE

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

Please See Extra Sheet.

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X, P	US 5,811,393 A (KLAGSBRUN et al) 22 September 1998, Figures 1 and 4, col. 36, lines 40-45.	19-24
A	TANAKA et al. Heparin-binding epidermal growth factor-like growth factor mRNA expression in neonatal rat brain with hypoxic/ischemic injury. Brain Research. 1999, Vol. 827, pages 130-138.	1-18
A	FABER-ELMAN et al. Involvement of wound-associated factors in rat brain astrocyte migratory response to axonal injury: in vitro stimulation. J. Clin. Invest. January 1996, Vol. 97, No. 1, pages 162-171.	1-18

[X] Further documents are listed in the continuation of Box C. [ ] See patent family annex.

*	Special categories of cited documents:	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A"	document defining the general state of the art which is not considered to be of particular relevance	"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"E"	earlier document published on or after the international filing date	"Y"	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"L"	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"&"	document member of the same patent family
"O"	document referring to an oral disclosure, use, exhibition or other means		
"P"	document published prior to the international filing date but later than the priority date claimed		

Date of the actual completion of the international search 17 NOVEMBER 1999	Date of mailing of the international search report 09DEC1999
Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703) 305-3230	Authorized officer CHRISTINE SAOUD Telephone No. (703) 308-0196

Form PCT/ISA/210 (second sheet)(July 1992)★

INTERNATIONAL, SEARCH REPORT

International application No.
PCT/US99/18022

A. CLASSIFICATION OF SUBJECT MATTER:
IPC (6):

A61K 38/16, 38/18, 38/19; C07K 14/00, 14/475, 14/485, 14/495, 14/52

B. FIELDS SEARCHED
Electronic data bases consulted (Name of data base and where practicable terms used):

APS, MEDLINE, EMBASE, CAPLUS
search terms: CNS, injury, EGF, heparin-binding EGF, hb-egf, ischem?, cDNA, isolat?

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US99/18022

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	SMITH et al. Macrophage/microglia regulatin of astrocytic tenascin: synergistic action of transforming growth factor-β and basic fibroblast growth factor. J. Neurosci. 15 December 1997, Vol. 17, No. 24, pages 9624-9633.	1-18

PATENT COOPERATION TREATY

JPF

From the INTERNATIONAL SEARCHING AUTHORITY

To: J. PETER FASSE
FISH AND RICHARDSON, P.C.
225 FRANKLIN STREET
BOSTON, MA 02110-2804

RECEIVED
DEC 13 1999
FISH & RICHARDSON, P.C.
BOSTON OFFICE

PCT

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL SEARCH REPORT OR THE DECLARATION

(PCT Rule 44.1)

Applicant's or agent's file reference 00786/400WO0	Date of Mailing (day/month/year) 09 DEC 1999
International application No. PCT/US99/18022	FOR FURTHER ACTION See paragraphs 1 and 4 below
Applicant THE GENERAL HOSPITAL CORPORATION	International filing date (day/month/year) 06 AUGUST 1999

Docketed By Practice Systems
(ISA TO IPT 21900 (expired)
Initials LXA
Record:

1. [X] The applicant is hereby notified ~~that the international search report has been~~ established and is transmitted herewith.

Filing of amendments and statement under Article 19:
The applicant is entitled, if he so wishes, to amend the claims of the international application (see Rule 46):

When? The time limit for filing such amendments is normally 2 months from the date of transmittal of the international search report; however, for more details, see the notes on the accompanying sheet.

Where? Directly to the International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland
Facsimile No.: (41-22) 740.14.35

DOCKETED BY BILLING SECRETARY
Due Date
Deadline
Fee

For more detailed instructions, see the notes on the accompanying sheet.

2. [ ] The applicant is hereby notified that no international search report will be established and that the declaration under Article 17(2)(a) to that effect is transmitted herewith.

3. [ ] **With regard to the protest** against payment of (an) additional fee(s) under Rule 40.2, the applicant is notified that:

[ ] the protest together with the decision thereon has been transmitted to the International Bureau together with the applicant's request to forward the texts of both the protest and the decision thereon to the designated Offices.

[ ] no decision has been made yet on the protest; the applicant will be notified as soon as a decision is made.

4. **Further action(s):** The applicant is reminded of the following:

Shortly after **18 months** from the priority date, the international application will be published by the International Bureau. If the applicant wishes to avoid or postpone publication, a notice of withdrawal of the international application, or of the priority claim, must reach the International Bureau as provided in rules 90 *bis* 1 and 90 *bis* 3, respectively, before the completion of the technical preparations for international publication.

Within **19 months** from the priority date, a demand for international preliminary examination must be filed if the applicant wishes to postpone the entry into the national phase until 30 months from the priority date (in some Offices even later).

Within **20 months** from the priority date, the applicant must perform the prescribed acts for entry into the national phase before all designated Offices which have not been elected in the demand or in a later election within 19 months from the priority date or could not be elected because they are not bound by Chapter II.

Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703) 305-3230	Authorized officer CHRISTINE SAOUD Telephone No. (703) 308-0196

Form PCT/ISA/220 (January 1994)★

(See notes on accompanying sheet)

INTERNATIONAL, SEARCH REPORT

International application No.
PCT/US99/18022

A. CLASSIFICATION OF SUBJECT MATTER:
IPC (6):

A61K 38/16, 38/18, 38/19; C07K 14/00, 14/475, 14/485, 14/495, 14/52

B. FIELDS SEARCHED
Electronic data bases consulted (Name of data base and where practicable terms used):

APS, MEDLINE, EMBASE, CAPLUS
search terms: CNS, injury, EGF, heparin-binding EGF, hb-egf, ischem?, cDNA, isolat?

NOTES TO FORM PCT/ISA/220

These Notes are intended to give the basic instructions concerning the filing of amendments under Article 19. The Notes are based on the requirements of the Patent Cooperation Treaty and of the Regulations and the Administrative Instructions under that Treaty. In case of discrepancy between these Notes and those requirements, the latter are applicable. For more detailed information, see also the PCT Applicant's Guide, a publication of WIPO.

In these Notes, "Article", "Rule" and "Section" refer to the provisions of the PCT, the PCT Regulations and the PCT Administrative Instructions, respectively.

INSTRUCTIONS CONCERNING AMENDMENTS UNDER ARTICLE 19

The applicant has, after having received the international search report, one opportunity to amend the claims of the international application. It should however be emphasized that, since all parts of the international application (claims, description and drawings) may be amended during the international preliminary examination procedure, there is usually no need to file amendments of the claims under Article 19 except where, e.g. the applicant wants the latter to be published for the purposes of provisional protection or has another reason for amending the claims before international publication. Furthermore, it should be emphasized that provisional protection is available in some States only.

What parts of the international application may be amended ?

The claims only.

The description and the drawings may only be amended during international preliminary examination under Chapter II.

When ? **Within 2 months from the date of transmittal of the international search report or 16 months from the priority date, whichever time limit expires later. It should be noted, however, that the amendments will be considered as having been received on time if they are received by the International Bureau after the expiration of the applicable time limit but before the completion of the technical preparations for international publication (Rule 46.1).**

Where not to file the amendments ?

The amendments may only be filed with the International Bureau and not with the receiving Office or the International Searching Authority (Rule 46.2).

Where a demand for international preliminary examination has been/is filed, see below.

How ? Either by cancelling one or more entire claims, by adding one or more new claims or by amending the text of one or more of the claims as filed.

A replacement sheet must be submitted for each sheet of the claims which, on account of an amendment or amendments, differs from the sheet originally filed.

All the claims appearing on a replacement sheet must be numbered in Arabic numerals. Where a claim is cancelled, no renumbering of the other claims is required. In all cases where claims are renumbered, they must be renumbered consecutively (Administrative Instructions, Section 205(b)).

What documents must/may accompany the amendments ?

Letter (Section 205(b)):

The amendments must be submitted with a letter.

The letter will not be published with the international application and the amended claims. It should not be confounded with the "Statement under Article 19(1)" (see below, under "Statement under Article 19(1)").

The letter must indicate the differences between the claims as filed and the claims as amended. It must, in particular, indicate, in connection with each claim appearing in the international application (it being understood that identical indications concerning several claims may be grouped), whether

(i) the claim is unchanged;
(ii) the claim is cancelled;
(iii) the claim is new;
(iv) the claim replaces one or more claims as filed;
(v) the claim is the result of the division of a claim as filed.

WHAT IS CLAIMED IS:

1. A method for regulating the levels of nerve growth factor in the central nervous system of a subject comprising administering an effective amount of a cytokine to the subject.

2. The method according to claim 1 in which the level of nerve growth factor is increased.

3. The method according to claim 2 in which the subject has a neurologic disorder.

4. The method according to claim 3 in which the neurologic disorder comprises dementia.

5. The method according to claim 3 in which the neurologic disorder comprises Alzheimer's disease.

6. The method according to claim 3 in which the neurologic disorder comprises damage to the nervous system due to trauma.

7. The method according to claim 3 in which the neurologic disorder comprises damage to the nervous system due to ischemia.

8. The method according to claim 3 in which the neurologic disorder comprises damage to the nervous system due to toxic agents.

9. The method according to claim 3 in which the neurologic disorder comprises damage to the nervous system due to infection.

10. The method according to claim 3 in which the neurologic disorder comprises damage to the nervous system due to malignancy.

11. The method according to claim 3 in which the neurologic disorder comprises a neurodegenerative disorder.

12. The method according to claim 3 in which the neurologic disorder comprises a congenital disorder.

13. The method according to claim 3 in which the neurologic disorder comprises a learning disorder.

14. The method according to claim 2 in which the cytokine is interleukin 1.

15. The method according to claim 2 in which the cytokine is fibroblast growth factor.

16. The method according to claim 2 in which the cytokine is tumor growth factor alpha.

17. The method according to claim 2 in which the cytokine is tumor growth factor beta.

18. The method according to claim 2 in which the cytokine is platelet derived growth factor.

19. The method according to claim 2 in which the cytokine is epidermal growth fact r.

20. The method according to claim 2 in which the cytokine is insulin-like growth factor I.

21. The method according to claim 2 in which the cytokine is insulin-like growth factor II.

22. The method of claim 14, 15, 16 or 17 in which the method of administration comprises intracerebroventricular injection.

23. The method according to claim 1 in which the level of nerve growth factor is decreased.

24. The method according to claim 23 in which the subject has a neurologic disorder.

25. The method according to claim 24 in which the neurologic disorder comprises a neurodegenerative disorder.

26. A method for regulating the levels of nerve growth factor in the central nervous system of a subject comprising administering to a subject an effective amount of a substance which alters the levels of a cytokine, which cytokine alters the level of nerve growth factor.

27. The method according to claim 26 in which the level of nerve growth factor is increased.

28. The method according to claim 26 in which the level of nerve growth factor is decreased.

29. The method according to claim 27 or 28 in which the subject has a neurologic disorder.

30. The method according to claim 29 in which the substance is an inhibitor of interleukin-1.

31. The method according to claim 30 in which the substance is a glucocorticoid.

32. The method according to claim 31 in which the substance is dexamethasone.

33. A method of controlling the expression of a protein or peptide of interest comprising exposing a recombinant construct comprising (a) the NGF promoter, or a responsive portion thereof, and (b) a nucleotide sequence encoding the protein or peptide of interest, to a substance which regulates the expression of NGF.

34. The method according to claim 33 in which the protein or peptide of interest is NGF.

35. The method according to claim 33 in which the protein or peptide of interest is BDNF.

36. The method according to claim 33 in which the protein or peptide of interest is CNTF.

37. The method according to claim 33 in which the protein or peptide of interest is neurotrophin-3 (NT-3).

38. The method according to claim 33 in which the protein or peptide of interest is a peptide or protein homologous to at least about six amino acids of NGF.

39. The method according to claim 33 in which the protein or peptide of interest is a peptide or protein homologous to at least about six amino acids of BDNF.

40. The method according to claim 33 in which the protein or peptide of interest is a peptide or protein homologous to at least about six amino acids of NT-3.

41. The method according to claim 33 in which the protein or peptide of interest is a peptide or protein homologous to at least about six amino acids of CNTF.

42. The method according to claim 33 in which the protein or peptide of interest is an enzyme.

43. The method according to claim 33 in which the protein or peptide of interest is choline acetyltransferase.

44. The method of claim 33, 34, 35, 36, 37, 38 39, 40, 41, 42, or 43 in which the substance which regulates the expression of NGF is transforming growth factor beta 1.

45. The method of claim 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, or 43 in which the substance which regulates the expression of NGF is interleukin 1.

46. The method of claim 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, or 43 in which the substance which regulates the expression of NGF is fibroblast growth factor.

47. The method of claim 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, or 43 in which the substance which regulates the expression of NGF is transforming growth factor beta

48. The method of claim 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, or 43 in which the substance which regulates the expression of NGF is epidermal growth factor.

49. A recombinant nucleic acid molecule comprising the NGF promoter, or a responsive portion thereof, and a nucleotide sequence encoding a protein or peptide of interest which is not nerve growth factor.

50. The recombinant nucleic acid molecule of claim 49 in which the protein or peptide of interest is brain derived growth factor.

51. The recombinant nucleic acid molecule of claim 49 in which the protein or peptide of interest is ciliary neurotrophic factor.

52. The recombinant nucleic acid molecule of claim 49 in which the protein or peptide of interest is neurotrophin-3.

53. An organism containing the recombinant nucleic acid molecule of claim 49, 50, 51, or 52.

54. The organism of claim 53 which is a bacterium.

55. The organism of claim 53 which is a yeast.

56. The organism of claim 53 which is a eukaryotic cell.

57. The organism of claim 53 which is a non-human transgenic animal.

58. Use of an effective amount of a cytokine, especially of a cytokine according to claims 14 to 21, for regulating the levels of nerve growth factor in the central nervous system of a subject.

FIG.1a

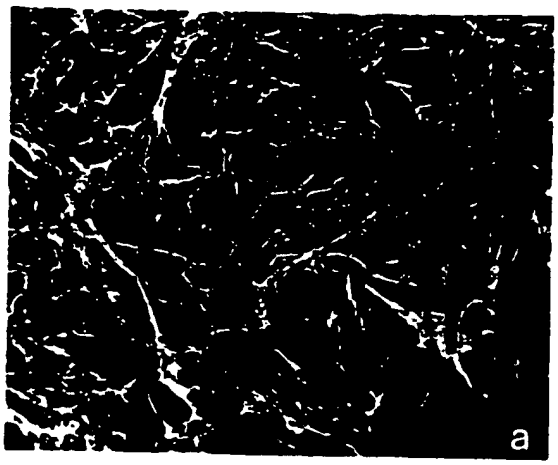


FIG. 1b

FIG. 1c

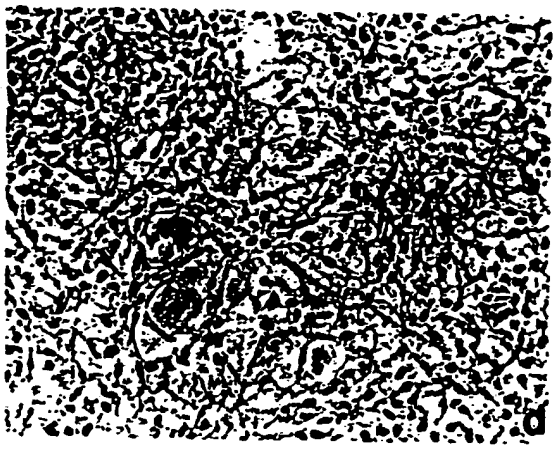


FIG. 1d

FIG. 2b

FIG. 2d

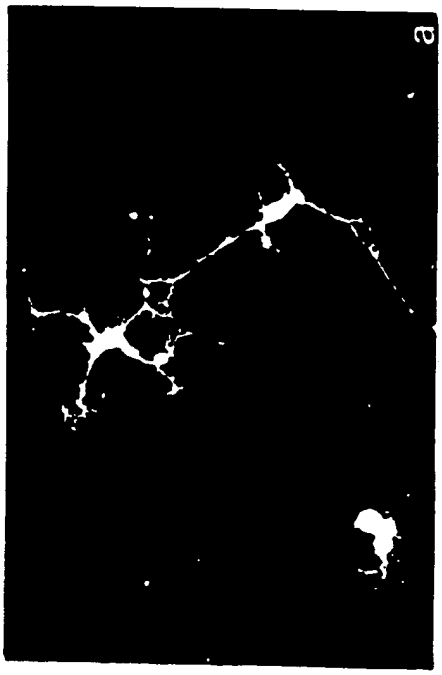


FIG. 2a

FIG. 2c

TENT COOPERATION TRE Y

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

To:

Assistant Commissioner for Patents
United States Patent and Trademark Office
Box PCT
Washington, D.C.20231
ETATS-UNIS D'AMERIQUE

in its capacity as elected Office

Date of mailing (day/month/year) 03 May 2000 (03.05.00)	
International application No. PCT/US99/18022	**Applicant's or agent's file reference** 00786/400WO1
International filing date (day/month/year) 06 August 1999 (06.08.99)	**Priority date** (day/month/year) 07 August 1998 (07.08.98)
Applicant FINKLESTEIN, Seth, P.	

1. The designated Office is hereby notified of its election made:

[X] in the demand filed with the International Preliminary Examining Authority on:

07 March 2000 (07.03.00)

[ ] in a notice effecting later election filed with the International Bureau on:

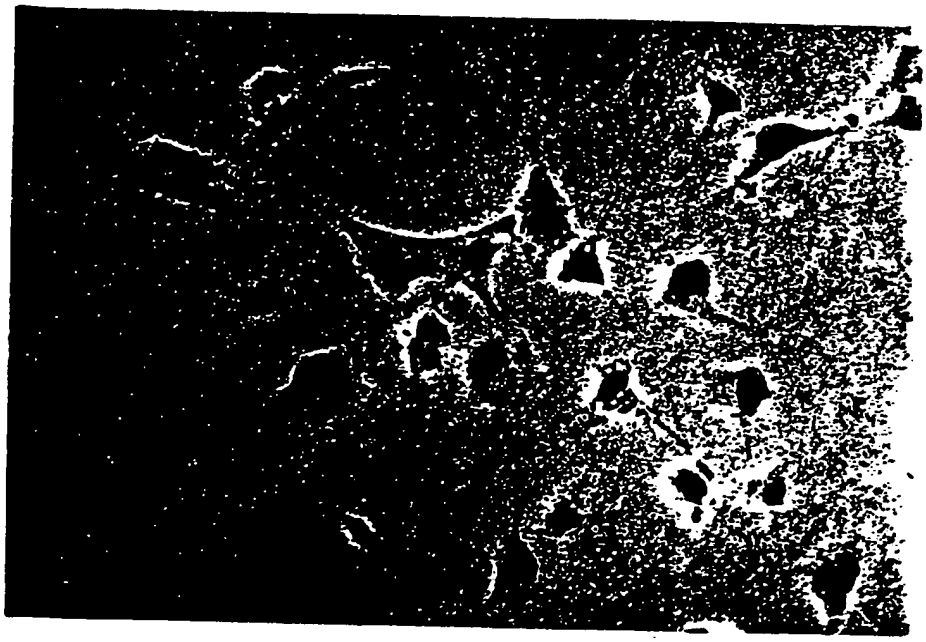
2. The election [X] was

[ ] was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO **34, chemin des Colombettes** **1211 Geneva 20, Switzerland**	Authorized officer Claudio Borton
Facsimile No.: (41-22) 740.14.35	Telephone No.: (41-22) 338.83.38

FIG. 3a



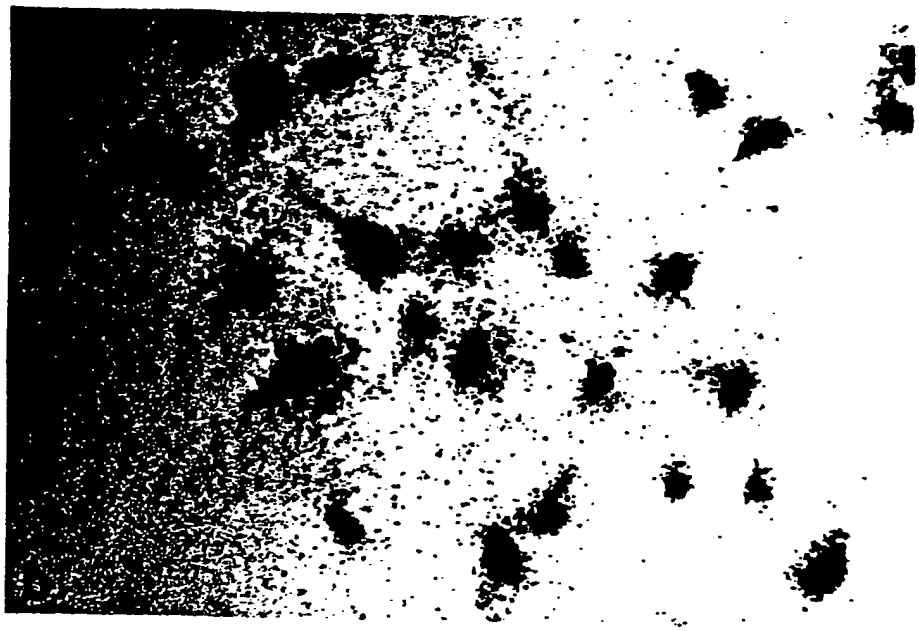


FIG. 3b

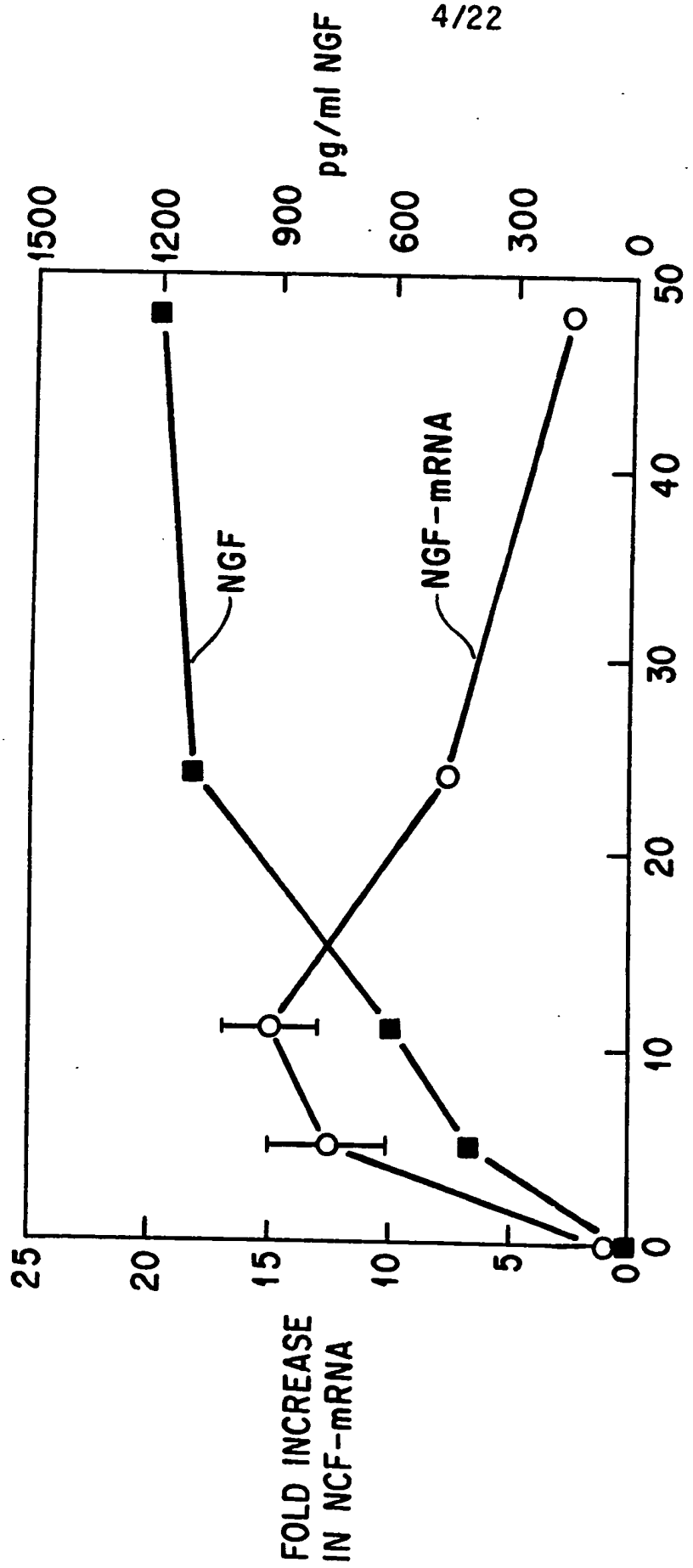

pg/ml NGF
1500
1200
900
600
300
0
NGF
NGF-mRNA
0
10
20
30
40
50
HOURS INCUBATION WITH 10% FCS
FOLD INCREASE IN NCF-mRNA
25
20
15
10
5
0

FIG. 4

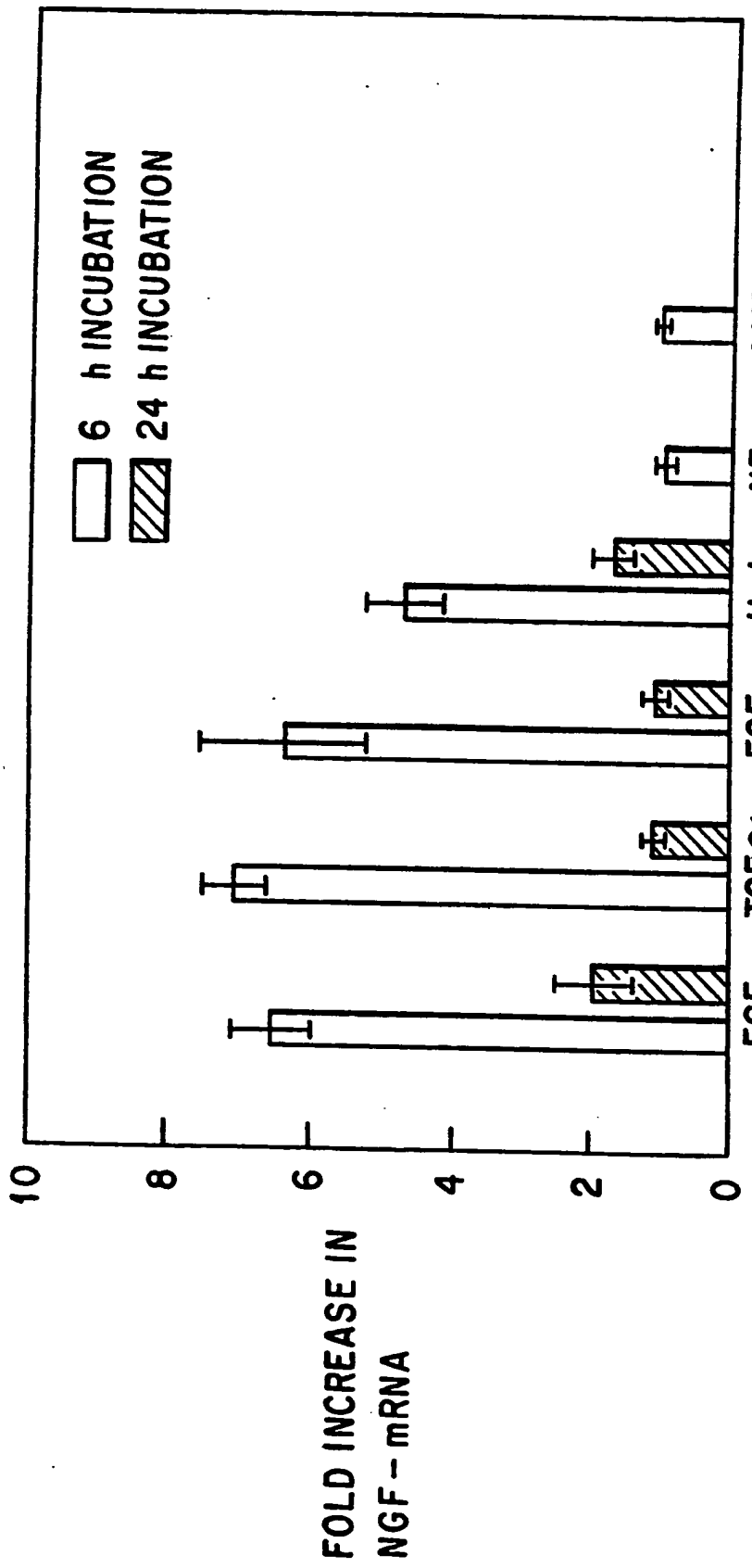

6 h INCUBATION
24 h INCUBATION
FOLD INCREASE IN NGF-mRNA
0
2
4
6
8
10
EGF
TGFα
FGF
IL-1
NE
cAMP

FIG. 5

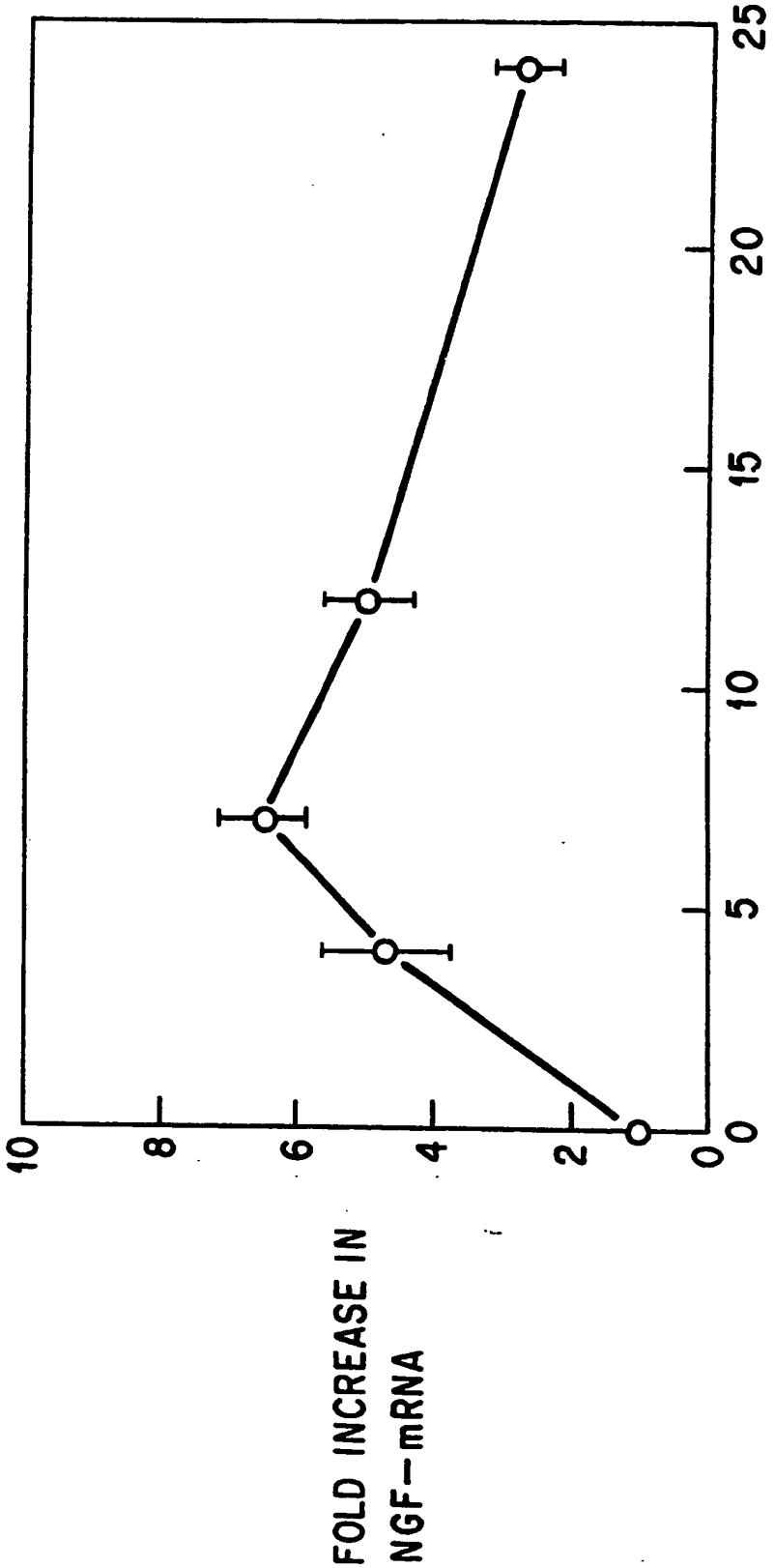

FOLD INCREASE IN NGF—mRNA
0
2
4
6
8
10
0
5
10
15
20
25
HOURS INCUBATION WITH IL-1

FIG. 6

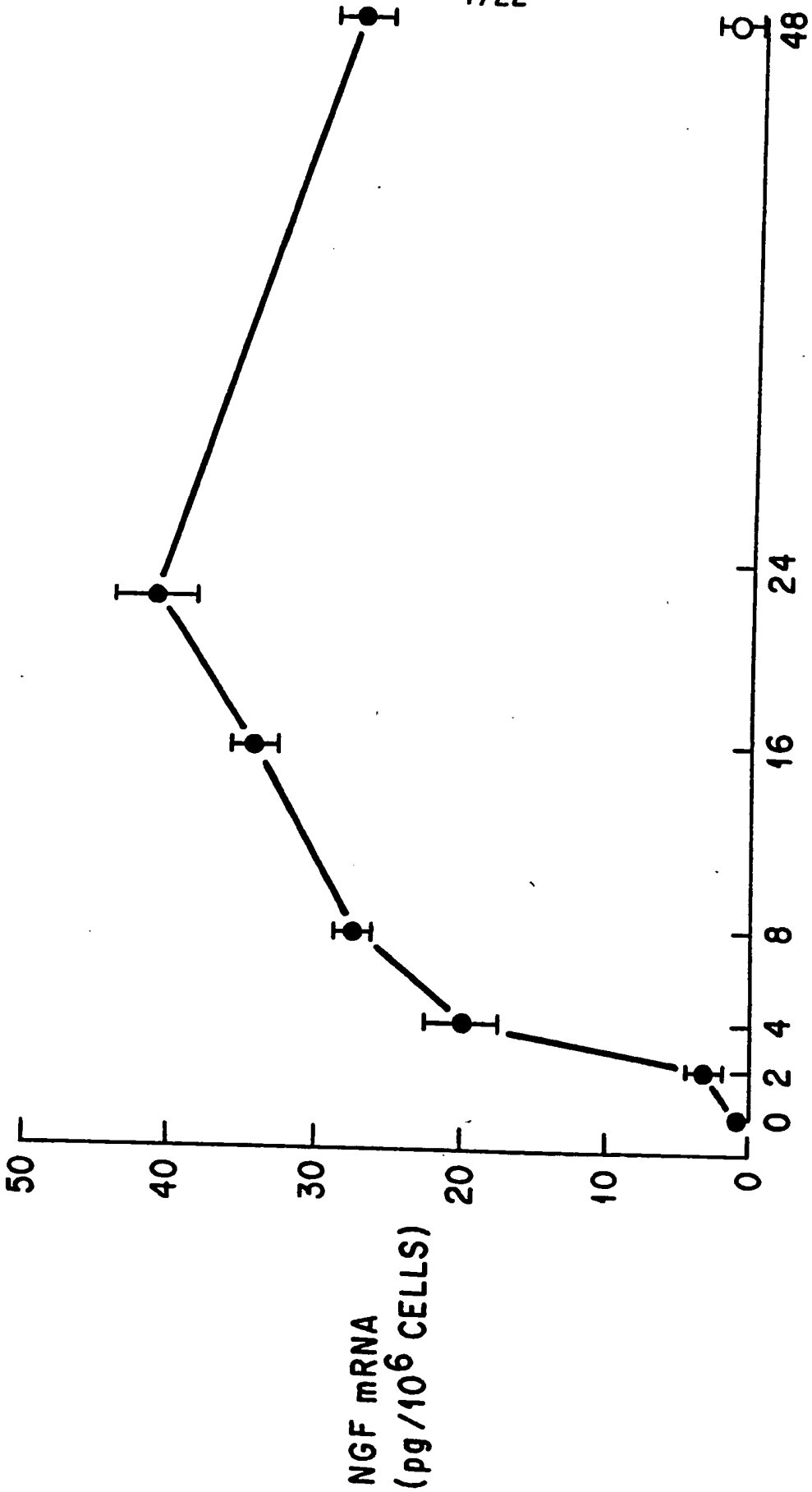


FIG. 7

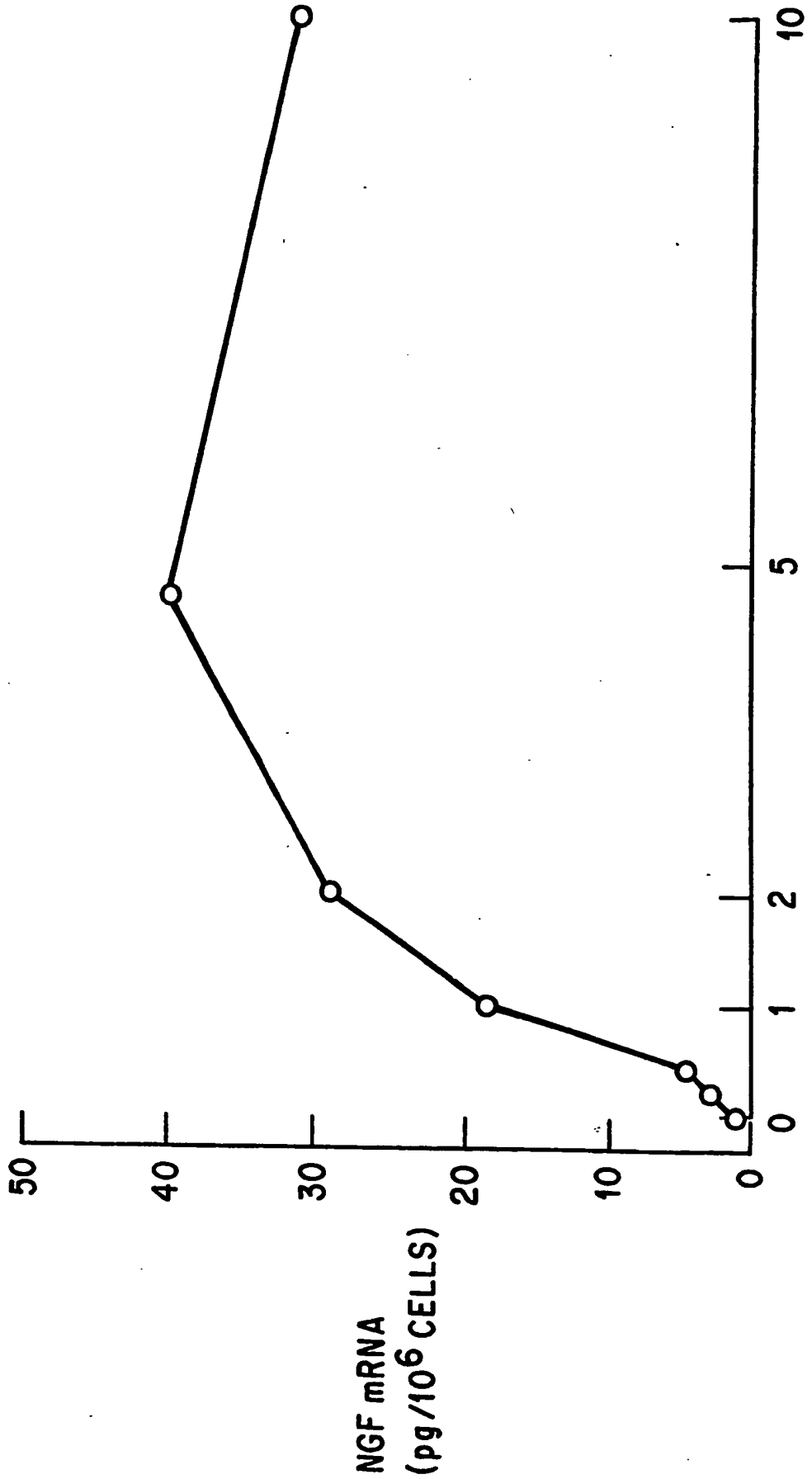


FIG. 8

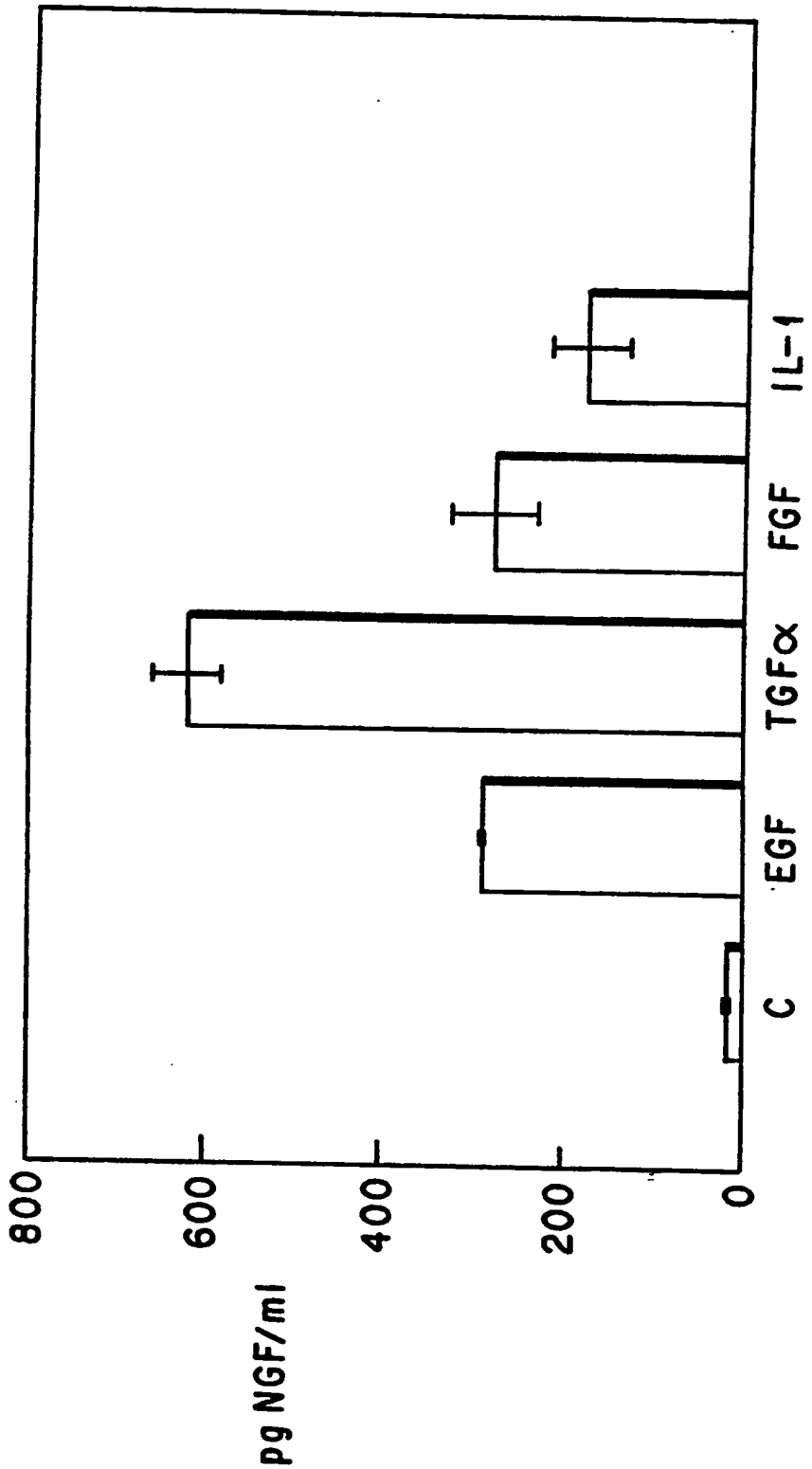


FIG. 9

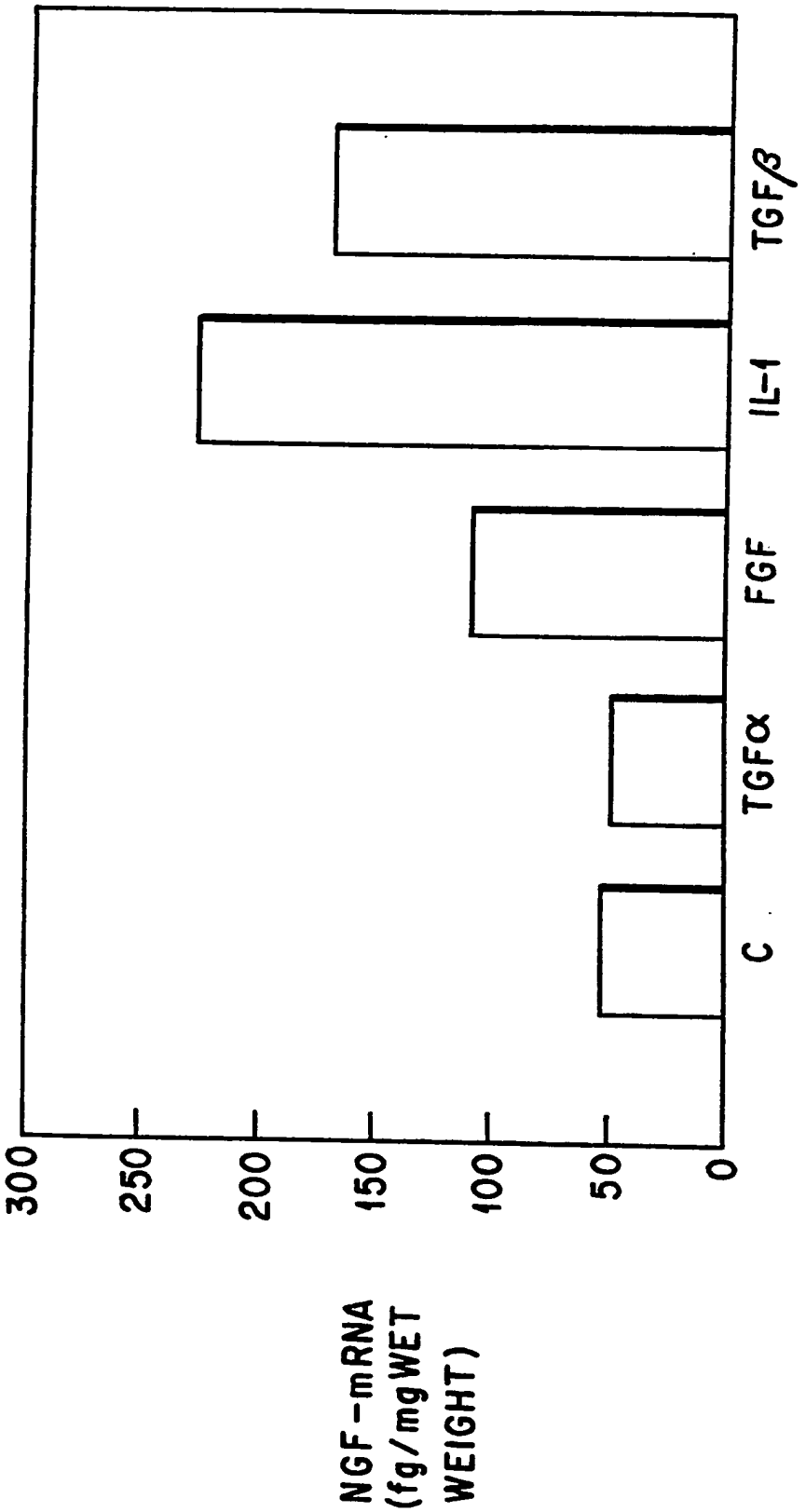

NGF-mRNA (fg/mg WET WEIGHT)
300
250
200
150
100
50
0
C
TGFα
FGF
IL-1
TGFβ

FIG. 10

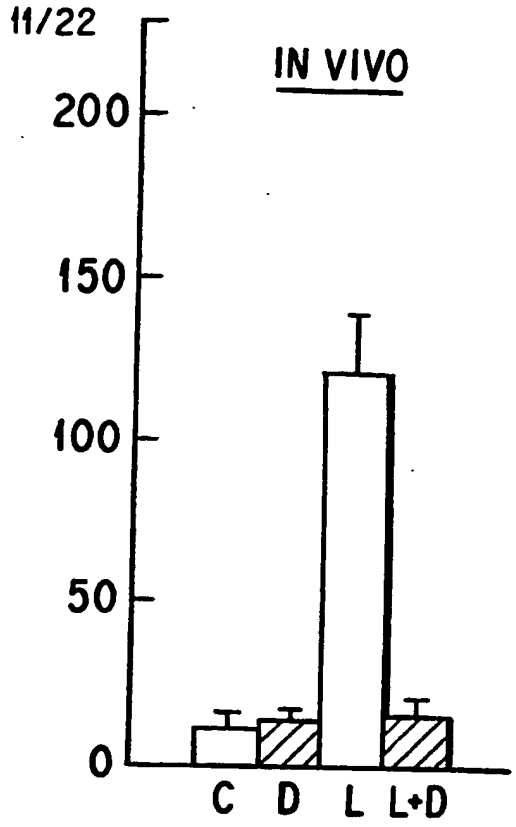


FIG. 11A

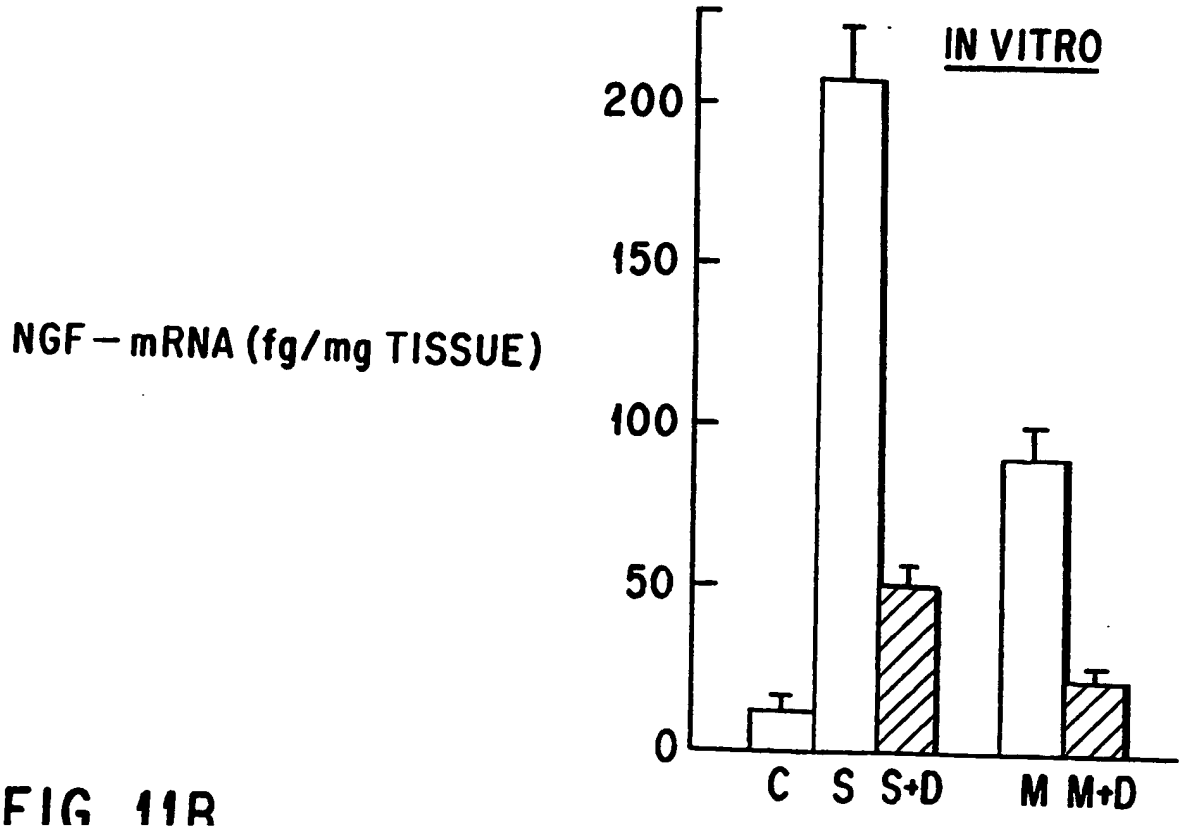


FIG. 11B

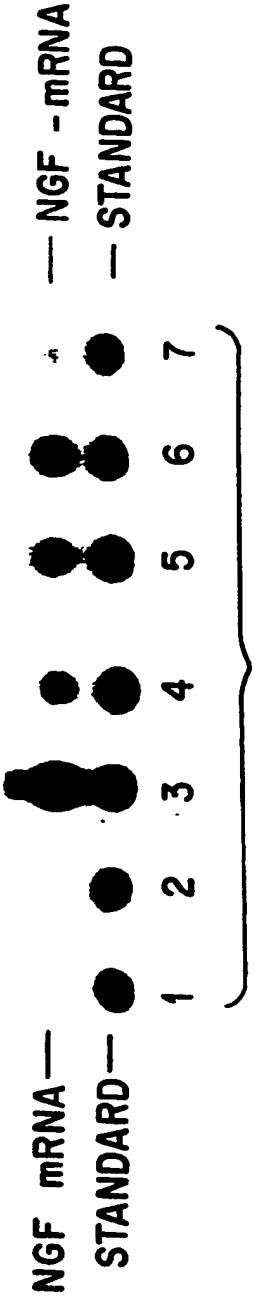


FIG. 12

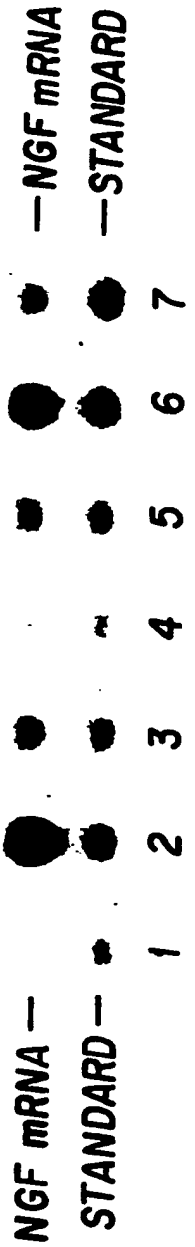


FIG. 13

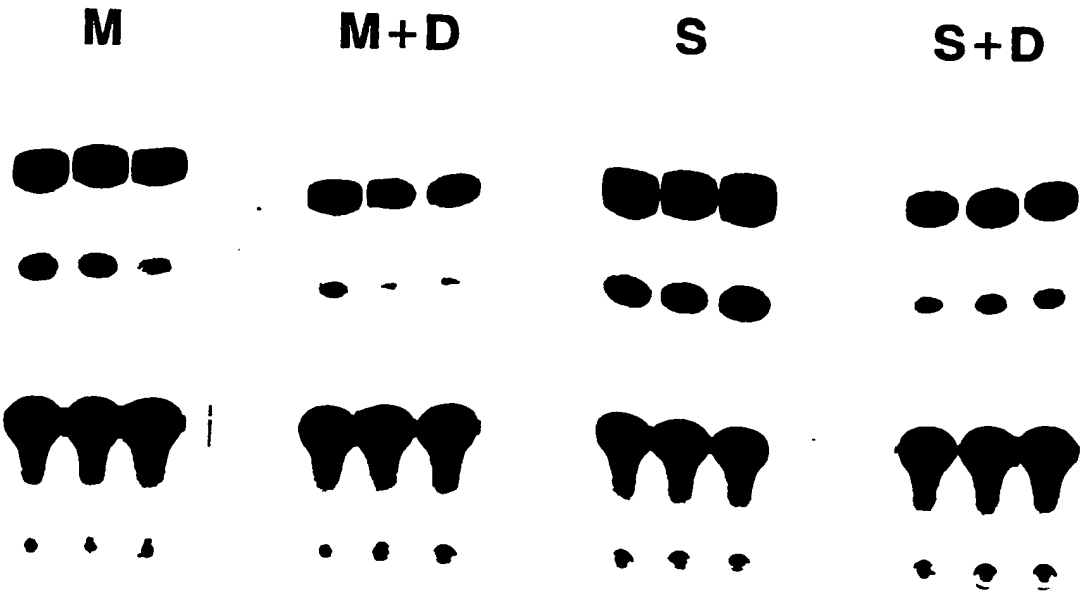


FIG. 14A

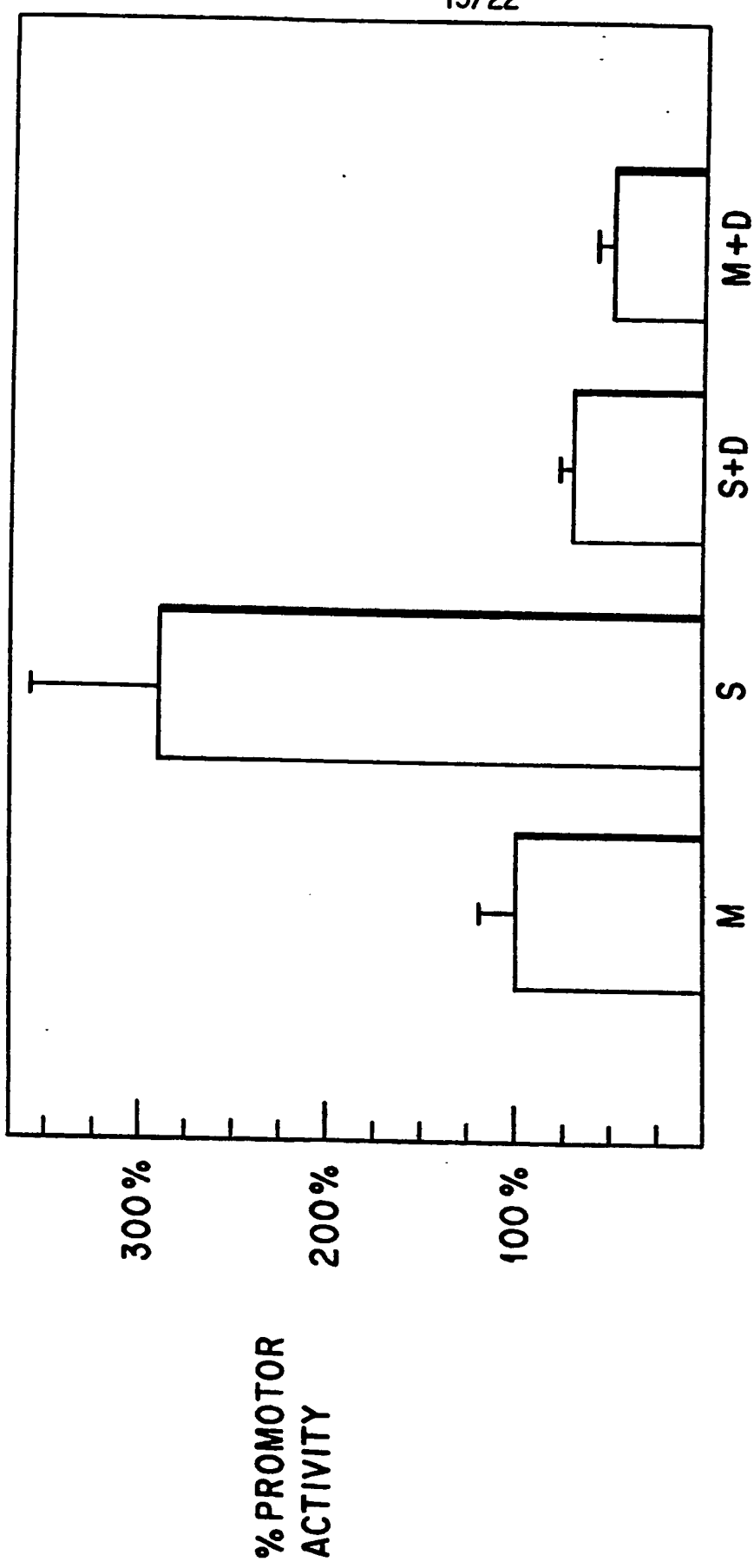


FIG. 14B

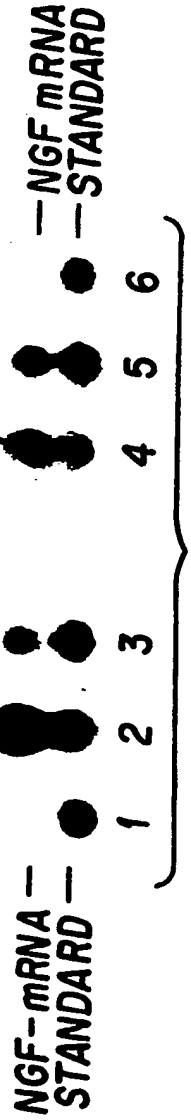


FIG. 15

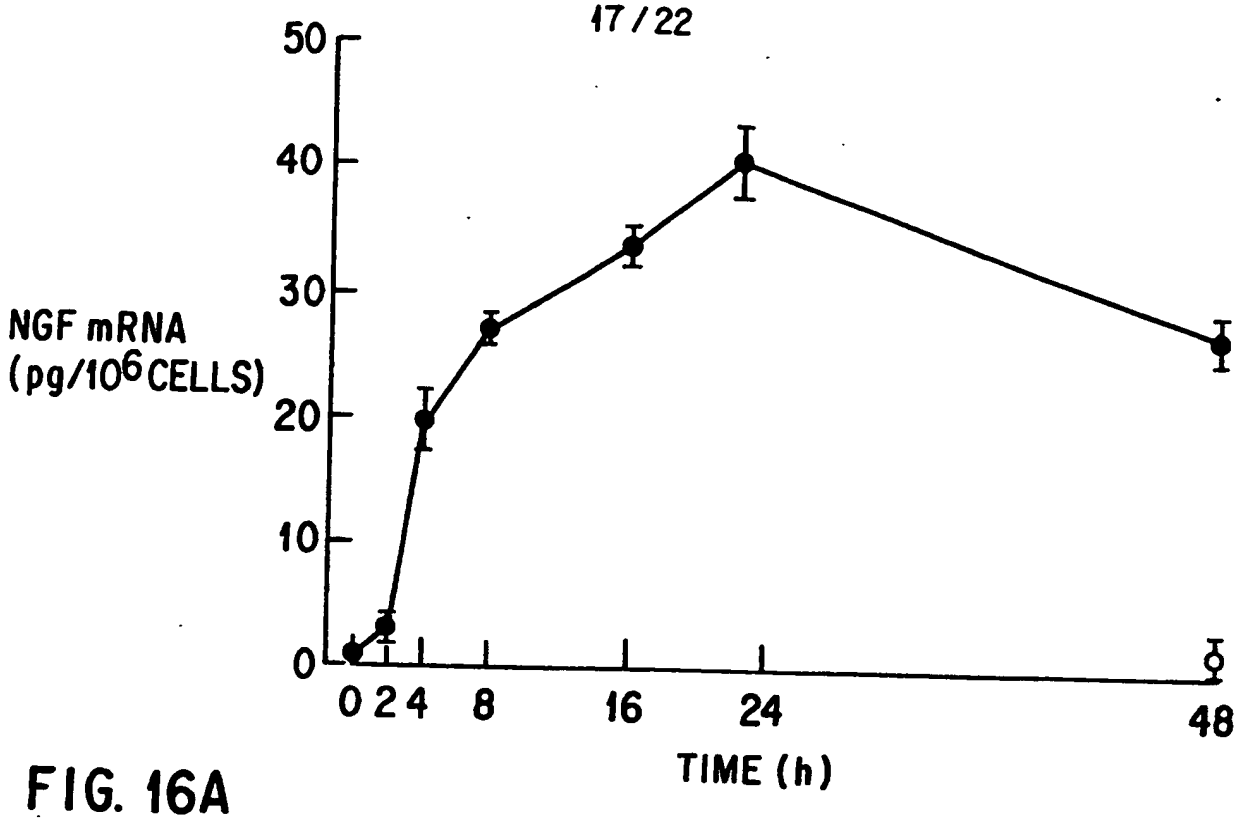


FIG. 16A

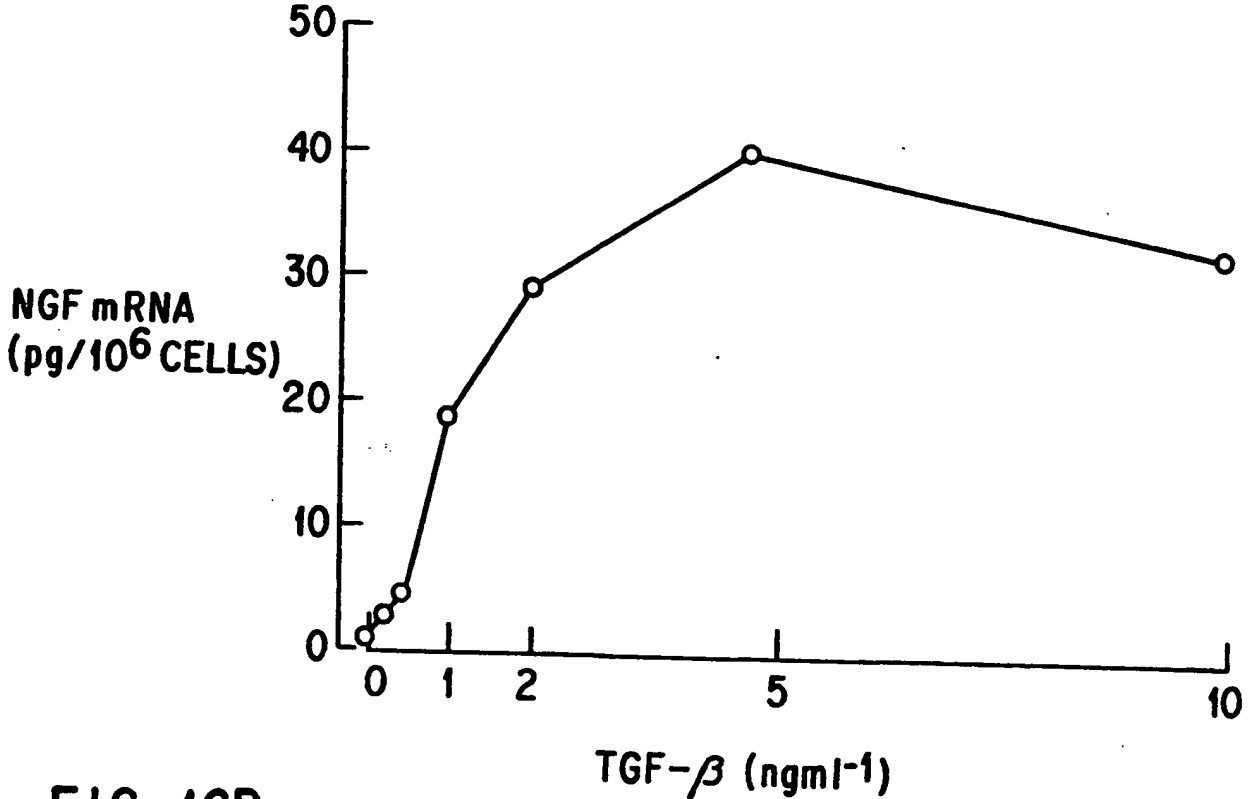


FIG. 16B

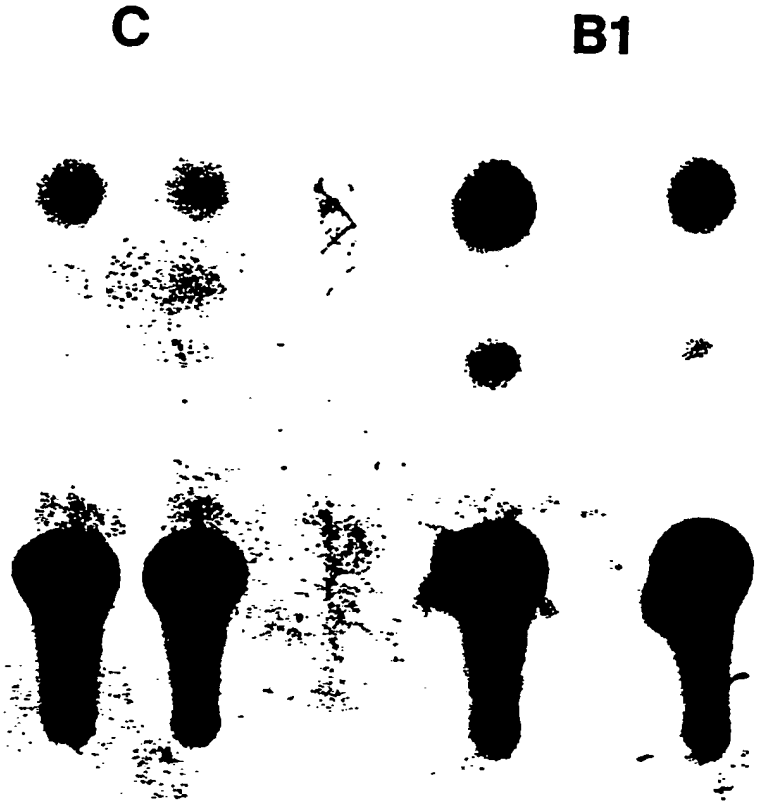


FIG. 17

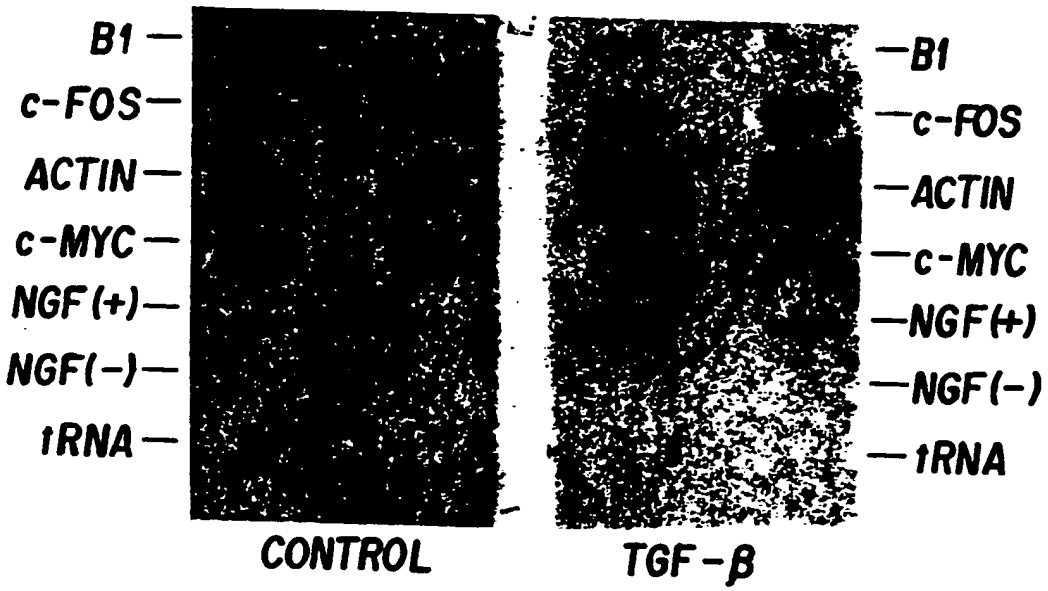

B1
c-FOS
ACTIN
c-MYC
NGF(+)
NGF(-)
tRNA
CONTROL
TGF-β
B1
c-FOS
ACTIN
c-MYC
NGF(+)
NGF(-)
tRNA

FIG.-18

FIG. 19B

FIG. 19A

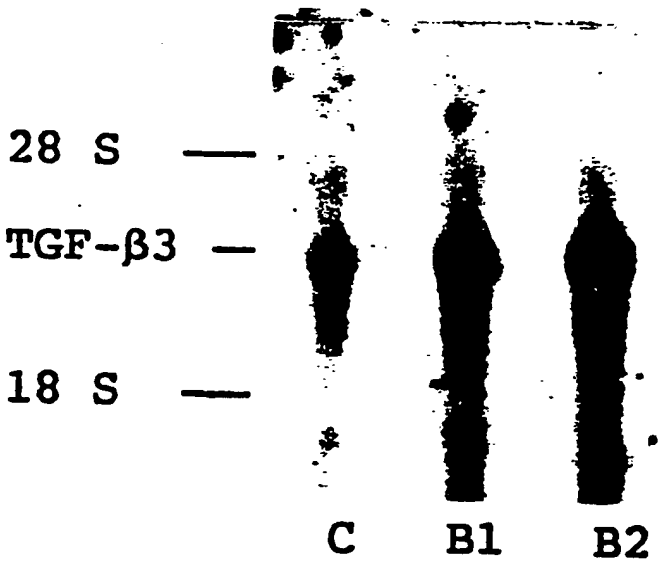


FIG. 20

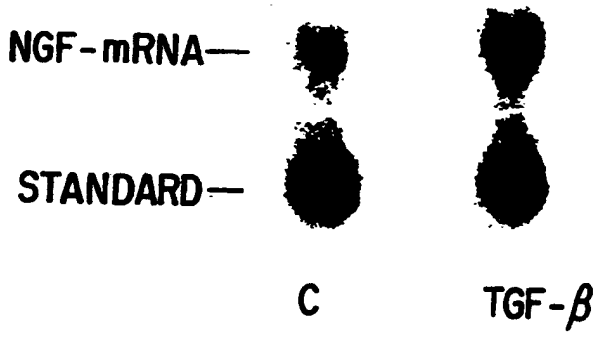


FIG. 21

INTERNATIONAL SEARCH REPORT

International Application No PCT/EP 90/01232

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) [6]

According to International Patent Classification (IPC) or to both National Classification and IPC

IPC[5]: C 12 N 15/67, C 12 N 1/21, C 12 N 5/10, C 12 N 15/00, C 12 N 15/16

II. FIELDS SEARCHED

Minimum Documentation Searched [7]

Classification System	Classification Symbols
IPC[5]	C 12 N

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched [8]

III. DOCUMENTS CONSIDERED TO BE RELEVANT [9]

Category *	Citation of Document, [11] with indication, where appropriate, of the relevant passages [12]	Relevant to Claim No. [13]
P,X	Proc. Natl. Acad. Sci. USA, vol. 87, May 1990, B. Hengerer et al.: "Lesion-induced increase in nerve growth factor mRNA is mediated by c-fos", pages 3899-3903 see the whole article cited in the application	33,43,49,53, 56
X	Molecular Brain Research, vol. 3, 1988, Elsevier Science Publishers B.V., M. Zheng et al.: "Structural and functional analysis of the promoter region of the nerve growth factor gene", pages 133-140 see the whole article	49,53,56
Y		33
Y	WO, A, 89/02472 (AMRAD CORP. LTD) 23 March 1989 see the whole document; particularly claims 1-5	33

* Special categories of cited documents: [10]

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
29th October 1990	28. 11. 90
International Searching Authority	**Signature of Authorized Officer**
EUROPEAN PATENT OFFICE	F.W. HECK

FURTHER INFORMATION C NTINUED FROM THE SEC ND SHEET

V. [X] OBSERVATIONS WHERE CERTAIN CLAIMS WERE FOUND UNSEARCHABLE [1]

This international search report has not been established in respect of certain claims under Article 17(2) (a) for the following reasons:

1. [X] Claim numbers *, because they relate to subject matter not required to be searched by this Authority, namely:

*claims 1-32,58
see PCT Rule 39.1(iv)

2. [ ] Claim numbers ....., because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. [ ] Claim numbers ....., because they are dependent claims and are not drafted in accordance with the second and third sentences of PCT Rule 6.4(a).

VI. [ ] OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING [2]

This International Searching Authority found multiple inventions in this international application as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims of the international application.

2. [ ] As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims of the international application for which fees were paid, specifically claims:

3. [ ] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claim numbers:

4. [ ] As all searchable claims could be searched without effort justifying an additional fee, the International Searching Authority did not invite payment of any additional fee.

Remark on Protest

[ ] The additional search fees were accompanied by applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

ANNEX TO THE INTERNATIONAL SEARCH REPORT ON INTERNATIONAL PATENT APPLICATION NO. EP 9001232 SA 38870

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report. The members are as contained in the European Patent Office EDP file on 09/11/90
The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO-A- 8902472	23-03-89	AU-A- 2524888	17-04-89
		EP-A- 0391911	17-10-90